REMARKS

Claims 1-5 and 7-21 were pending in the present application prior to this communication. By virtue of this response, claims 9, 11, and 14 have been amended and new claims 22-47 have been added to define Applicants' invention with greater particularity. Accordingly, claims 1-5 and 7-47 are currently under consideration. Support for new and amended claims can be found, for example, on page 10, line 13; page 12, lines 1-3; and page 8, line 19 to page 9, line 4. No new matter is believed to have been added. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2.

With respect to claim amendments and cancellation, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants acknowledge with appreciation withdrawal of all previous claim rejections set forth in the Office Action mailed November 17, 2004.

Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 1-5 and 7-21 under 35 U.S.C § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, is respectfully traversed. Specifically, Applicants respectfully disagree with the Examiner's assertion that the limitation "about" in the claims is a relative term, which allegedly renders the claims indefinite.

It is well established that the use of a relative term does not render a claim indefinite under 35 U.S.C. §112, second paragraph. *See Seattle Box Co. v. Indus. Crating & Packaging, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984) (stating that the fact that the claim language,

including terms of degree, may not be precise, does not automatically render the claim indefinite); *see also* MPEP §2173.05(b). Moreover, the term "about" is accepted and widely used in patent practice and is clearly acceptable under the law. *See, e.g., Modine Mfg. Co. v. Int'l Trade Comm'n*, 75 F.3d 1545, 37 USPQ2d 1609 (Fed. 1996) (finding the phrase "about 0.015-0.040" definite); *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1346 (Fed. Cir. 2005) (holding that the term "about" in a claim reciting "administering about 70 mg of" a drug have the ordinary meaning "approximately"). The Patent Office consistently allows claims reciting the term "about" and "[t]he propriety of the use of the expression 'about' in claims to permit 'of some tolerance' is established by long practice in the Patent Office." *Ex parte King*, 82 U.S.P.Q. (BNA) 450, 451 (Bd. Pat. App. & Int. 1948).

A search of the U.S. Patent and Trademark Office Database on December 2, 2005 revealed that the Patent Office has issued 753,331 patents having at least one claim with the word "about;" 197,521 of which were issued on or after January 1, 2000. Furthermore, the Patent Office continues to issue patents whose claims recite the term "about" in reference to a numerical range. *See, e.g.*, U.S. Patent Nos. 6,970,414; 6,970,748; 6,970,383; 6,969,914; 6,969,781; 6,969,759; 6;969,579; 6,969,529; 6,969,521; 6,969,483; and 6,969,418, issued on November 29, 2005; U.S. Pat. Nos. 6,967,865; 6,967,827; 6,967,227; 6,967,225; and 6.967,218, issued on November 22, 2005; U.S. Patent Nos. 6,965,156; 6,965,056; 6,965,043; 6,965,035; 6,964,942; 6,964,816; 6,964,776; 6,964,626; and 6,964,302, issued on November 15, 2005. The Patent Office therefore does not find that the recitation of the term "about" in reference to a numerical range *ipso facto* renders a claim indefinite as to the upper and lower limit of the range.

In addition, the Examiner has examined cases which have issued as patents wherein the term "about" is used in a manner similar to how it is used in the present claims, that is, in the recitation of a numerical range of a drug dose or amount. For example, claim 1 of U.S. Patent No. 6,906,047 (issued on June 14, 2005) recites the term "about" in reference to a numerical range indicating the ratio of a drug to a buffer in a pharmaceutical composition. In U.S. Patent

No. 6,586,458 (issued on July 1, 2003), claim 7 recites the term "about" in reference to the range of the dose of a drug that is administered to a patient. Similarly, in U.S. Patent No. 6,121,276 (issued on September 19, 2000), claim 10 recites "about" in reference to the range of the dose of a drug that is administered to a patient. In U.S. Patent No. 6,184,208 (issued on February 6, 2001), claim 5 recites "about" in reference to the range of the percentage of a peptide in a pharmaceutical composition.

In view of the above remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103

The rejection of claims 1-5 and 7-21 under 35 U.S.C. §103(a) as allegedly being unpatentable over WO 9406422 (WO '422) is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that it allegedly would have been obvious to one of ordinary skill in the art to further modify the teaching of WO '422 to come to the present invention.

As acknowledged by the Examiner, WO '422 does not disclose administration of a sub-therapeutic dose in the range of about 1% up to about 20% of the conventionally administered amount. As further acknowledged by the Examiner, WO '422 does not disclose local administration of paclitaxel, nor the claimed length of treatment.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a prima *facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Third, there must be a reasonable expectation of success. MPEP

§2143. Applicants respectfully submit that none of these requirements has been met. Based on the failure to meet any one of these requirements, a *prima facie* case of obviousness has not been established; therefore, the rejection should be withdrawn.

Applicants further submit that the Examiner has not shown a suggestion to modify WO '422 to come to the presently claimed invention and that the obviousness rejection may be properly withdrawn on this ground.

Applicants respectfully disagree with the Examiner's assertion that, since WO '422 allegedly discloses that low doses of paclitaxel results in fewer adverse side effects and reduces the chance of developing mdr paclitaxel resistance, it allegedly would have been obvious to one of ordinary skill in the art to "further modify the reference such that the resulting amount is effective to maintain efficacy in the treatment of the cancer while reducing unwanted side effects and development of mdr resistance." WO '422 teaches a single regimen, i.e., administration of paclitaxel as a 96 hour continuous infusion with a dose level of between 70 and 140 mg/m^2. Thus, the only low dosage contemplated by the reference is dose levels between 70-140 mg/m^2. The reference is completely silent and makes no suggestion to lower the dosage further, much less to the presently claimed sub-therapeutic dose levels. Moreover, the reference makes no suggestion that any lower dose levels would maintain efficacy for the desired purpose. Furthermore, the Examiner has presented the alleged motivation to modify WO '422 as an unsupported statement. Absent the teaching of the present invention, one of ordinary skill in the art would not have been motivated to further reduce the dosages taught by WO '422 to reach the sub-therapeutic dose levels required by the present claims.

Applicants further disagree with the Examiner's assertion that "since the length of treatment is related to the efficacy of the overall treatment, it would have been obvious to one of ordinary skill in the art to further modify the length of treatment in WO '422 such that therapeutic levels of paclitaxel are achieved without the undesirable side effects." As discussed

above, the only length of treatment disclosed by WO '422 is a 96 hour continuous infusion of paclitaxel as the "prolonged exposure regimen" or the "long term exposure." There is no disclosure or even suggestion provided by this reference to lengthen the treatment time. The reference is completely silent about further modifying the length of treatment. Furthermore, Applicants respectfully submit that the Examiner has not provided any basis supporting the statement that the length of treatment is related to the efficacy of the overall treatment. Absent the teaching of the present invention, one of ordinary skill in the art would not have been motivated to further modify the length of treatment disclosed in WO '422.

Similarly, as discussed in the previous response to Office Action, WO '422 contemplates systemic administration of paclitaxel and provides no teaching or suggestion for local administration of paclitaxel. The Examiner has provided no support for the statement that one of ordinary skill in the art would have been motivated to modify the teaching of WO '422 to replace systemic administration with local administration.

Accordingly, Applicants respectfully submit that there is no suggestion to further modify WO '422 to arrive at the present invention and that the obviousness rejection may be properly withdrawn on this ground.

For the same reasons elaborated above, the Examiner has failed to show that the cited reference teaches or suggests all the claim limitations. The obviousness rejection may also be properly withdrawn on this ground.

Without the requisite teaching or suggestion in the cited reference to arrive at the present invention, Applicants respectfully submit that there is insufficient basis for reasonable expectation of success. The obviousness rejection may be properly withdrawn on this ground.

Applicants further submit that the case law relied on by the Examiner is inapplicable to the present case. *In re* Geisler, 116 F.3d 1465, 43 USPQ2d. 1362 (Fed. Cir. 1997) involves a

patent application in which the claimed thickness range of 50 to 100 Angstroms for the protective layer overlaps at its end point with the thickness range of 100 to 600 Angstrom disclosed by the cited reference. *Id.* at 1467. The court stated that the claims were *prima facie* obvious. *Id.* at 1469. In the present case, by contrast, the dosage range disclosed in WO '422 and the claimed dosage range are significantly different. As explained in the previous response to Office Action, the dose levels contemplated by WO '422 (i.e., 70-140 mg/m^2) represent in the range of about 50% to greater than 100% of the conventionally administered amount of the active agent, which, as the instant specification discloses, typically falls in the range of about 135-175 mg/m^2. The present claims, on the other hand, recite a sub-therapeutic dose level of about 1% to about 20% of the conventionally administered level.[1]

Similarly, *In re Aller*, 220 F.2d 454, 105 USPQ 233 (CCPA 1955), which states that "it is not inventive to discover the optimum or workable ranges by routine experimentation"[2] is also inapplicable to the present invention. That case involved routine optimization of temperature and acid concentration in a chemical reaction. As explained in a later CCPA case cited by the Examiner, *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977), the rule stated in *In re Aller* does not apply when "the parameter optimized was not recognized to be a result-effective variable."[3] *Id.* at 620. The court in *In re Antonie* emphasized that the controlling question is whether the differences between the prior art and the claimed invention as a whole are such that the invention as a whole would have been obvious. *Id.*

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[1] Independent claims 11 and 14 have now been amended to recite "about 1% to about 10%" of the conventionally administered level.

[2] A later CCPA case has expressed reservation about this rule. *In re Yates*, 663 F.2d 1054, 211 USPQ 1149 (CCPA 1981). It states, "such 'rule of patentability' (and ever-lengthening list of exceptions which they engender) is that they tend to be cloud the ultimate legal issue – obviousness – and exalt the formal exercise of squeezing new factual situations into preestablished pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103." *Id.* at 1055, n4.

[3] The court states that this is another exception to the rule set forth in *In re Aller* in addition to the exception of unexpected results. In re Antonie at 620.

When viewed as a whole, it is not obvious to further reduce the already "low" dosage taught in WO '422 to arrive at the present invention. The mere fact that a lower dosage of pharmacologically active agent might produce less side effects would not motivate a person skilled in the art to further reduce the dosage disclosed in WO '422 to effect treatment of cancer, particularly in view of the teaching in WO '422 that the dosage disclosed therein is already low and already solves the problems of side effects. See, for example, abstract and page 5, lines 1-24.

Accordingly, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and request that this rejection be withdrawn.

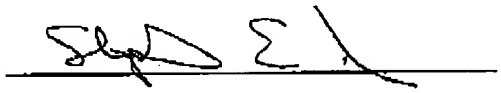
Moreover, this rejection is not applicable to new claims 22-47 for the reasons set forth above.

Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: December 8, 2005

By 

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